PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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18. OKT. 2004
FRIST:

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	14.10.2004
Applicant's or agent's file reference R 42192	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/08933	12.08.2003	12.08.2002

Applicant
IGENEON KREBS-IMMUNTHERAPIE FORSCHUNGS- U... et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference R 42192	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08933	International filing date *(day/month/year)* 12.08.2003	Priority date *(day/month/year)* 12.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K39/395		
Applicant IGENEON KREBS-IMMUNTHERAPIE FORSCHUNGS- U... et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.03.2004	14.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Wagner, R Telephone No. +49 89 2399-7357

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08933

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-32 as originally filed

Claims, Numbers

1-22 received on 28.09.2004 with letter of 28.09.2004

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☐ claims Nos.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 14, 17 regarding industrial applicability

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6,9-22
	No:	Claims	1-5,7,8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-13,15,16,18-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to industrial applicability

Claims 14 and 17 appear to relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.

1. Reference is made to the following documents:

   D1: Dimitri Flieger et al., Cancer Immunol. Immunother, 2000, vol. 49; pp: 441-448.
   D2: Kim et al., Vaccine, 19 (2001) 530-537.
   D3: WO 0135989
   D4: WO 00/06605
   D5: Di Carlo et al., Oncology Reports, Vol. 8: 387-392, 2001
   D6: Gratsa et al., Anticancer Research, 17: 4111-4118, 1997
   D7: Nanashima et al., J. Hepatobiliary Pancreat. Surg. (1999) 6: 391-395

2. In D3 (examples 5 and 6) the applicants isolate anti-idiotype antibodies, which mimic EPCAM and Lewis antigens. According to the present description **(see page 17, last paragraph)** anti-idiotype antibodies are considered as antigens i.e. are an embodiment of the invention. In D3, the anti-idiotype antibodies are used in a pharmaceutical composition for vaccinating monkeys by subcutaneous administration (example 4). It appears that the vaccine preparation of D3 is also suitable for intravenous administration. Therefore D3 anticipates the subject-matter of claims 1-5, 7, 8 (Article 33(2) PCT).

3. D4 (example 3, page 52) discloses a hetero miniantibody which comprises an single chain antibody specific against Lewis-Y and a single chain antibody specific against CD80, which is a cell surface antigen present in peripheral blood

monocytes and dendritic cells. As the present claims encompass components that can be linked (see description page 17, first paragraph) and as the present claims do not exclude linking of two antibodies the subject-matter of claims 1-4 and 7 is anticipated by D4 (Article 33(2) PCT).

4. The subject-matter of claim 6 is new (Article 33(2) PCT), because the prior art does not disclose a combination for the treatment of cancer comprising one of the receptors specified in claim 6. As the present application does not provide any substantive support for a possible synergistic effect due to the combination of an antigen of the EGF receptor family, CD55 receptor, transferrin receptor and P-glycoprotein with a tumour-associated carbohydrate, the subject-matter of claim 6 cannot be considered to involve an inventive step (Article 33(3) PCT).

5. Claims 9-13 are directed to the use of a kit comprising a tumour associated antigen and a tumour associated carbohydrate or antibodies directed against said antigens (see Further Remarks, section 1) for the determination of a cancer tumor cells. Such a use of a kit is not disclosed in the prior art.
D5 (page 392) discloses that the use of an antibody MAb B3 directed against Lewis ^{y} and the determination of CEA may be very useful in addition to the histological grading and staging liver metastases of colorectal tumours. D5 does not disclose how CEA is determined, but CEA is either determined by a an immunological method, requiring and anti-CEA antibody or by other methods, which require the use of the CEA antigen as standard. By following the teaching of D5, the skilled person inevitably will use the antibody Mab B3 and either an anti-CEA antibody or an anti-CEA antigen as standard. The provision of said components in a kit and it's use in a diagnostic method does not involve an inventive step (Article 33(3) PCT). The detection of cancer cells in different bodily tissues does not confer an inventive step to the use, therefore the subject- matter of claims 9, 10, 11, 13, 19 does not involve an inventive step (Article 33(3) PCT).

6. Claims 20-23 are directed to a diagnostic agent based on a kit comprising a tumour associated antigen and a tumour associated carbohydrate or antibodies directed against said antigens (see Further Remarks, section 1) and further comprising a reagent for determining the immune reaction. As D5 suggests the use of an antibody to determine the Lewis antigen, and as the additional features of claims 20-23 are only directed to commonly used elements in immunoassays, the subject-matter of claims 20-23 does not involve an inventive step (Article 33(3)

PCT).

7. In addition it must be underlined that Claims 9-13 and 20-23 are directed to the combined diagnostic use of tumour associated surface antigens and a tumour associated carbohydrates or antibodies directed against said antigens (see Further Remarks, section 1). The present application does not disclose that any technical problem can be solved by said combination in general. The only data provided relate to the combined use of anti- EPCAM and anti- Lewis^y antibodies for the detection of said antigens in breast cancer. The results of section C of example 1 and in figure 1 show merely that the co-expression of EPCAM and Lewis^y correlates with the a reduced survival time. Said correlation cannot be extrapolated to any combination of any cellular surface protein with an aberrant protein glycosylation epitope. It appears therefore that the determination of the co-expression solves a technical problem only for the combination of the determination of an EPCAM and a Lewis epitope. An inventive step can therefore not be acknowledged to the subject-matter of present claims 9-13 and 20-23. See also item 2 under Further Important Remarks.

8. Claims 14-18 refer to a "neoepitope" which according to the description is to be understood as an epitope formed by the tumour associated surface protein and by the tumour associated carbohydrate and being specifically recognized by a single antibody. As the present application does not disclose how such an epitope or antibody residing at the interface between a surface protein and a carbohydrate can be obtained, the technical effect on which the evaluation of the presence or absence of an inventive step could be based is lacking. Therefore an inventive step cannot be acknowledged for the subject-matter of claims 15-19 (Article 33(3) PCT).

9. In case the claimed priority would not be valid, the document classified as PX in the search report would be relevant.

Further important Remarks:

1. Claim 1 is not supported (Article 6 PCT) and not sufficiently disclosed (Article 5 PCT) because the application does not teach the skilled person how any cellular surface protein can be used to treat cancer. In the present opinion the cellular surface protein is considered to be a tumour associated antigen (taa - see page 2

of the description).

In addition item b) of claim 1 is not clear because the term "aberrant" is a relative term and requires the definition of the "normal" state. In the present written opinion the "aberrant glycosylation" is considered to be a tumour associated carbohydrate (see first paragraph of page 6), or aberrantly expressed carbohydrate.

2. Claims 9-13 and19-22 are directed to the combined diagnostic use of tumour associated surface antigens and a tumour associated carbohydrates or antibodies directed against said antigens (see Further Remarks, section 1). The present application provides only some data regarding the combination the diagnostic determination of EPCAM and Lewis^y antigens. No data were provided for any of the numerous possible combinations of tumour associated surface antigens and tumour associated carbohydrates. Therefore the subject-matter of claims 9-13, 19-22 is not supported by the description (Article 6 PCT) and not sufficiently disclosed (Article 5 PCT) over the entire width of the claimed scope but only regarding the combination EpCam - Lewis.

3. Claim 14 is not clear (Article 6 PCT) because it does not comprise any method steps and it does not define how the kit of claim 1 should be used.

4. Claim 10 is not clear (Article 6 PCT) because a diagnostic test is not considered as being a part of a medical treatment.

10. For the assessment of the present claims 14, 17 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a methods of diagnosis to be carried out on the human or animal body.

New Claims:

1. A kit for the combined use for the treatment of cancer patients, which set comprises the following components:
a) an antigen comprising at least one epitope of a cellular surface protein, or an antibody directed against the cellular surface protein, and
b) an antigen comprising at least one epitope of an aberrant protein glycosylation, or an antibody directed against the aberrant protein glycosylation.

2. A kit according to claim 1, characterized in that the components a) and b) are contained in one pharmaceutical preparation each or in a single pharmaceutical preparation suitable for immunotherapy.

3. A kit according to claim 2, characterized in that the pharmaceutical preparation is formulated as a vaccine.

4. A kit according to claim 2, characterized in that the pharmaceutical preparation is formulated as an intravenously tolerable product.

5. A kit according to any one of claims 1 to 4, characterized in that the antigen of component a) represents an epitope of a cellular adhesion protein, in particular of a protein selected from the group of EpCAM, NCAM and CEA.

6. A kit according to any one of claims 1 to 4, characterized in that the antigen of component a) is an epitope of a surface receptor, in particular a receptor molecule selected from the group of the EGF receptor family, CD55 receptor, transferrin receptor and P-glycoprotein.

7. A kit according to any one of claims 1 to 6, characterized in that the antigen of component b) represents an epitope of a carbohydrate selected from the group of Lewis antigens, in particular Lewis y and/or Lewis b, sialyl-Tn and Globo H.

8. A kit according to any one of claims 1 to 7, characterized in that the antigen of component a) represents an epitope of the EpCAM molecule or of the Her-2/neu receptor, and the antigen of component b) represents an epitope of the Lewis Y molecule.

9. The use of a kit according to claim 1 for preparing a diagnostic agent for the immunologic determination of tumor cells of a solid tumor or disseminated tumor cells of a cancer disease.

10. The use according to claim 9, characterized in that the determination is carried out within the scope of the treatment of cancer patients.

11. The use according to claim 9, characterized in that tumor cells from samples of peripheral blood or bone marrow are determined.

12. The use according to claim 9 or 10, characterized in that an antibody titer against the antigens of the components is determined.

13. The use according to claim 12, characterized in that the determination is carried out for monitoring a treatment of a cancer patient.

14. A method for immunologic selection of a tumor-specific target antigen or of antibodies directed against the target antigen by using a kit according to claim 1, characterized in that the antigen is a neoepitope which is formed by the glycosylation

of an antigen of component a) with an antigen of component b).

15. A preparation of an antigen which comprises a neoepitope or its mimic, obtainable by a method according to claim 14.

16. A preparation according to claim 15 wherein the antigen is a naturally occurring antigen or a fragment thereof.

17. A method according to claim 14, characterized in that an antibody directed against the neoepitope is selected and prepared by using a kit according to claim 1.

18. Preparation of an antibody with specificity for a neo-epitope, obtainable by a method according to claim 17.

19. A diagnostic agent based on a kit according to claim 1, characterized in that it contains a reagent for determining an immune reaction with components a) and b), or with antibodies against these.

20. An agent according to claim 19, characterized in that the reagent is labelled with a fluorescent agent, a chromogen, a radiolabel or an enzyme.

21. An agent according to claim 20, characterized in that the reagent is immobilized on a carrier.

22. An agent according to claim 21, characterized in that the carrier is a matrix for immunoaffinity chromatography.